REMARKS

FORMAL MATTERS:

Claims 16-18, 22-26, 30-34, 36, 40-44, 46-50, and 52-56 are pending after entry of the amendments set forth herein.

Claims 39, 45, and 51 have been canceled without prejudice.

Claims 16, 24, 30, 40-44, 46-50, and 52-56 have been amended. Support for these amendments is found in the claims as originally filed and throughout the specification at, for example: claim 16: cancelled claim 39; claim 24: cancelled claim 45; claim 30: cancelled claim 51; and claims 40-44, 46-50, and 52-56: page 18, line 24 through page 19, line 21.

No new matter has been added.

REJECTIONS UNDER §112, ¶1 (ENABLEMENT)

The Office Action maintains the rejection of Claims 16-18, 22-26, 30-34 and 36 under 35 U.S.C. § 112, 1st ¶ for an asserted lack of enablement. In view of the amendments to the claims, this rejection may be withdrawn.

In particular, the Office Action states that the specification is enabling for a method for directing the biodistribution of a drug that binds to a protein target by administering to a mammalian host a bifunctional molecule comprising a targeting moiety and a drug moiety, wherein the targeting moiety is a peptidyl-prolyl isomerase ligand.

In the spirit of expediting prosecution and without conceding as to the correctness of the rejection, claims 16, 24 and 30 have been amended to remove the objectionable language and to recite "wherein the targeting moiety is a peptidyl-prolyl isomerase ligand". Amended claims 16, 24, and 30 incorporate the limitations of claims 39, 45, and 51, respectively, which claims were not subject to the enablement rejection.

In view of the above, it is respectfully submitted that the rejection of Claims 16-18, 22-26, 30-34 and 36 under 35 U.S.C. § 112, 1st ¶ be withdrawn.

REJECTIONS UNDER §102

Forsgren et al. (Office Action, page 7)

Claims 24 and 26 have been rejected under 35 U.S.C. §102(b) for allegedly being anticipated by Forsgren et al. (Cancer Res., 39(12):5155-5164 (1979)) as evident by Asai et al. (Acta Endocrinol., 87(1):173-180 (1978)). In view of the amendments to the claims, this rejection may be withdrawn.

Forsgren et al. discloses a molecule consisting of a nitrogen mustard drug moiety linked to an estradiol -17 beta phosphate targeting moiety.

As noted above, claim 24 has been amended to incorporate the limitation of claim 45 and to recite the "targeting moiety is a **peptidyl-prolyl isomerase ligand**".

It is well established that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987), cert. denied, 481 U.S. 1052 (1987). See also, Scripps Clinic and Research Foundation v. Genentech, Inc., 18 USPQ 2d 1001 (Fed. Cir. 1991).

Since the cited reference fails to teach a **peptidyl-prolyl isomerase ligand** targeting moiety, the cited reference does not teach each and every element as recited in Claims 24-26. Accordingly, the Applicants respectfully request that this rejection be withdrawn.

Szepeshazi et al. (office Action, page 8)

The Office Action has maintained the rejection of Claims 16-18, 22-26, 30-34, and 36 under 35 U.S.C. § 102(b) for allegedly being anticipated by Szepeshazi et al. (Anticancer Drugs 8(10):974-987 (1997)) as evident by Nagy et al. (PNAS 93:2464-2469 (1996)), and Nagy et al. (PNAS 93:7269-7273 (1996)). In view of the amendments to the claims, this rejection may be withdrawn.

Szepeshazi et al. discloses a series of compounds comprising doxorubicin and the targeting moiety luteinizing hormone releasing hormone (LH-RH), such as AN-207 and AN-152.

As noted above, claims 16, 24 and 30 have been amended to recite "wherein the targeting moiety is a peptidyl-prolyl isomerase ligand". Amended claims 16, 24, and 30 incorporate the limitations of claims 39, 45, and 51, respectively, which claims were not subject to the enablement rejection.

Since the cited reference fails to teach a **peptidyl-prolyl isomerase ligand** targeting moiety, the cited reference does not teach each and every element as recited in Claims 16-18, 22-26, 30-34, and 36. Accordingly, the Applicants respectfully request that this rejection be withdrawn.

REJECTIONS UNDER §103(A)

Forsgren et al., Asia et al., Trouet et al. (Office Action, page 10)

Claims 24 and 25 have been rejected under 35 U.S.C. §103(a) for allegedly being unpatentable over Forsgren et al. (Cancer Res., 39(12):5155-5164 (1979)) as evident by Asai et al. (Acta Endocrinol., 87(1):173-180 (1978)), in view of Trouet et al., (PNAS, 79:626-629 (1982)). In view of the amendments to the claims, this rejection may be withdrawn.

Forsgren et al. discloses a bifunctional molecule consisting of a nitrogen mustard drug moiety linked to an estradiol -17 beta phosphate targeting moiety.

As noted above, claim 24 has been amended to incorporate the limitation of claim 45 and to recite the "targeting moiety is a **peptidyl-prolyl isomerase ligand**". Forsgren et al. fails to teach a **peptidyl-prolyl isomerase ligand** targeting moiety.

Since Trouet et al. has been cited solely for its disclosure of a linking group, it fails to make up the deficiency of Forgren et al., as detailed above. Therefore, since the combination of the references do not teach each and every element found in the claims, the combination of the

cited references fails to render the present claims obvious. Accordingly, the Applicants respectfully request that this rejection be withdrawn.

Forsgren et al., and WO 95/02684 (Office Action, page 12)

Claims 16-18, 22-23, 30-34, 36, and 39-56 have been rejected under 35 U.S.C. §103(a) for allegedly being unpatentable over Forsgren et al. (Cancer Res., 39(12):5155-5164 (1979)), in view of WO 95/02684. In view of the remarks made herein, this rejection may be withdrawn.

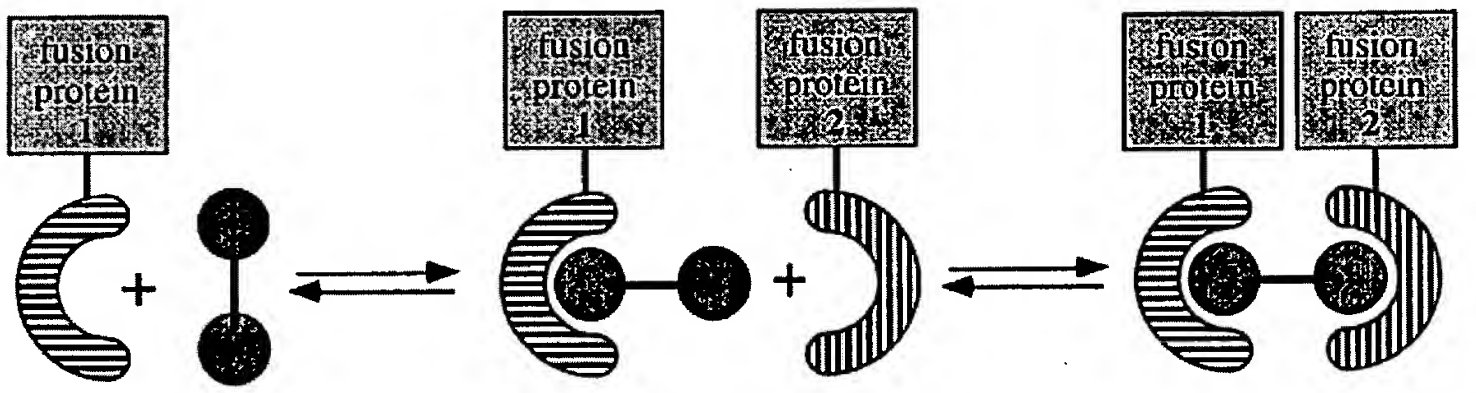
In maintaining the rejection, the Office Action asserts that it would have been obvious "to substitute the estrogen targeting moiety as taught by Forsgren et al for the targeting moiety such as peptidyl-prolyl isomerase ligand FK506 type ligand, cyclosporine and rampamycin ...as taught by the WO 95/02684" (Office Action, page 13). However, the Applicants respectfully disagree.

As developed in the analysis below, the Examiner's position is based on the incorrect reading of the recombinant proteins of WO 95/02684. Specifically, the Examiner's position is based on the incorrect assumption that the recombinant proteins include peptidyl-prolyl isomerase ligands

In particular, the Applicants stress that WO 95/02684 teaches a system that includes two elements: (1) chimeric proteins and (2) ligand molecules capable of oligomerizing the chimeric proteins (see page 3, lines 24-26). According to the cited reference, the chimeric protein includes a drug moiety and a targeting moiety. The cited reference further teaches that the targeting moiety of such chimeric proteins are "capable of **binding to** FK-506-type ligand, a cyclosporine A-type ligand, tetracycline or a steroid ligand" that are present in a cell and are referred to in the cited reference as oligomerization ligands (see page 4, lines 31-35, emphasis added). Therefore, the cited reference does not teach a moiety such as a peptidyl-prolyl isomerase ligand FK506 type ligand, cyclosporine and rampamycin as a targeting domain of a chimeric molecule, but instead teaches that such molecules can be **targeted, thereby inducing oligomerization in the cell.** In other words, the reference refers to receptors such as FK506, and

does not use ligands to those receptors for constructing bifunctional molecules (ligand plus drug) as claimed. Therefore substitution of the targeting moiety, as taught in WO 95/02684, with the targeting moiety of Forsgren et al., would not result in the claimed bifunctional molecule of the present invention.

As noted on page 14, line 32 of the cited reference, the concept for the inducible protein association is illustrated in Figure 12, reproduced below:



Immun-ophilin (fusion protein)	Dimeric ligand (HED/ HOD)	1:1 Complex: Modified effector domain prevents binding to calcineurin	2:1 Complex: Ligand-induced protein dimerization

The figure illustrates that the chimeric protein (indicated as the fusion protein) complexes with ligand molecule to form ologomerized complexes of the chimeric protein. The cited reference teaches use of **peptidyl-prolyl isomerase as a targeting domain of the chimeric protein and ligands of peptidyl-prolyl isomerase as inducing ologomerized complexes.**

> The Office Action asserts the following
>
> "WO 95/02684 publication teaches a bifunctional molecule such as fusion protein comprising **a targeting moiety such as various peptidyl-prolyl isomerase ligand linked to FAS** (see page 14, lines 1-6, in particular) and methods of making the same as a pharmaceutical."

(emphasis added, Office Action, page 15).

However, the Applicants respectfully disagree. The cited passage discloses a chimeric protein comprising FAS linked to the targeting moiety FKBP12. FKBP12 is a peptidyl-prolyl isomerase – **not the ligand of a peptidyl-prolyl isomerase**.

The Office Action further notes that the "reference targeting domain such as FK506, cyclosporine and rampamycin is the same targeting domain...as defined by the present specification" (Office Action, page 15).

Again, Applicants respectfully disagree. As previously noted, the disclosure of FK506, cyclosporine and rampamycin in WO 95/02684 is within the context of their use as oligomerizing ligands – not as targeting domains of bifunctional molecules. The cited passage, of the reference specifically states:

> **As discussed in greater detail later, and by way of example, in various embodiments of this invention the chimeric protein is capable of binding to an FK506-type ligand, a cyclosporin A-type ligand, tetracycline or a steroid ligand. Such binding leads to oligomerization of the chimeric protein with other chimeric protein molecules which may be the same or different.**

(Page 4, lines 31-35).

If, according to the cited passage, the chimeric protein is capable of binding to ligands such as FK506, cyclosporine and rampamycin, then the disclosed chimeric protein **cannot** have such compound as the targeting domain.

Moreover, the cited reference further provides on page 31, lines 1-3, that such a domain can be a FKBP and a cyclophilin **receptor** – not the ligand of such a receptor, as incorrectly stated in the Office Action. In the context of ologomerizing lands, the cited reference teaches ligands capable of binding to FKBPs (see page 35, line35-37).

Accordingly, the Applicants maintain that the cited reference does not teach use of ligands of peptidyl-prolyl isomerases as targeting moieties. If, *in arguendo*, one were to combine the teaching of WO 95/02684 with that of Forsgren et al., the result would be a bifunctional molecule having a drug moiety and a targeting moiety that is a **peptidyl-prolyl isomerase**, such

as FBKP12. In contrast, the pending claims are directed to a bifunctional molecule having a drug moiety and a targeting moiety that is a **ligand of a peptidyl-prolyl isomerase**. As such, the combination of the two references does not teach using a ligand of a peptidyl-prolyl isomerase as a targeting moiety.

Accordingly, the combination of the references fails to teach each and every limitation found in the claims of the present invention. Therefore, the combination of the cited references cannot render the present application obvious. As such, the Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-131.

Respectfully submitted,
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Date: Feb. 21, 2006

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